## STIC-ILL

**From:** Afremova, Vera
**Sent:** Wednesday, April 23, 2003 6:03 PM
**To:** STIC-ILL
**Subject:** 10/032,728

Hi, please, could I have these references:

1.
ACCESSION NUMBER: 2001336287 MEDLINE
TITLE: Pyruvate/dichloroacetate supply during reperfusion accelerates recovery of cardiac energetics and improves mechanical function following cardioplegic arrest.
AUTHOR: Smolenski R T; Amrani M; Jayakumar J; Jagodzinski P; Gray C C; Goodwin A T; Sammut I A; Yacoub M H
SOURCE: EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, (2001 Jun) 19 (6) 865-72.

2

ACCESSION NUMBER: 2002121773 MEDLINE
TITLE: Energetic stimulation of the heart.
AUTHOR: Hermann H P
SOURCE: CARDIOVASCULAR DRUGS AND THERAPY, (2001 Sep) 15 (5) 405-11.

3.
ACCESSION NUMBER: 85239005 MEDLINE
TITLE: The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation.
AUTHOR: McKnight C K; Elliott M J; Pearson D T; Holden M P; Alberti K G
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1985 Jul) 90 (1) 97-111.

4.
ACCESSION NUMBER: 85239005 MEDLINE
TITLE: The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation.
AUTHOR: McKnight C K; Elliott M J; Pearson D T; Holden M P; Alberti K G
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1985 Jul) 90 (1) 97-111

Vera Afremova
CM1 11E13
308-9351

J THORAC CARDIOVASC SURG 90:97-111, 1985

# The effects of four different crystalloid bypass pump-priming fluids upon the metabolic response to cardiac operation

**The crystalloid solutions used to prime cardiopulmonary bypass pumps frequently contain metabolically active substrates. However, there is a lack of controlled studies to investigate the metabolic response to cardiac operations using different pump primes. We have carried out a prospective, randomized study of 24 patients divided into four groups, each group receiving a different crystalloid prime. The primes contained glucose, lactate, glucose and lactate, or neither glucose nor lactate. Using identical anesthetic, surgical, and perfusion techniques, we estimated the metabolic response to cardiac operation in all patients by frequent blood sampling for measurement of hormone (insulin, glucagon, cortisol, and growth hormone) and metabolite concentrations (glucose, lactate, pyruvate, glycerol, alanine, and 3-hydroxybutyrate) from the day before operation to the seventh postoperative day. The results demonstrated that, after 4 hours postoperatively, the endocrine and metabolic response to cardiac operation was unaffected by the nature of the priming fluid. However, major endocrine and metabolic changes occurred before that time, which were related directly to the glucose and lactate contents of the prime. Very high concentrations of both glucose and lactate were observed at the end of bypass if they were included in the prime. Given the known dangers of hyperglycemia in cerebral ischemia and the potential gluconeogenic effects of infused lactate, we suggest that glucose-free and lactate-free primes be employed in the extracorporeal circuit.**

Charles K. McKnight, F.F.A.R.C.S., Martin J. Elliott, M.D., F.R.C.S., Derek T. Pearson, F.R.C.P., F.F.A.R.C.S., Michael P. Holden, F.R.C.S., and K. George M. M. Alberti, F.R.C.P., *Newcastle-Upon-Tyne, United Kingdom*

The metabolic response to cardiac operation has been studied extensively during the past 30 years. Despite this, there are wide differences in the reported alterations in blood hormone and metabolite concentrations. It has been shown that the use of different anesthetic[1,2] and extracorporeal perfusion[3-6] techniques can modify the metabolic response, as can the temperature at which cardiopulmonary bypass is conducted.[7] However, analysis of these papers reveals that a wide variety of pump primes have been employed. It is possible that the priming fluid used may itself modulate the response, since these fluids frequently contain large quantities of metabolically active substrates. There have been no controlled studies to investigate the effect of different crystalloid cardiopulmonary bypass pump-priming fluids on the metabolic response to cardiac operation. Thus, we have performed a prospective, randomized study to assess the changes that occur in blood concentrations of several hormones and intermediary metabolites during and after cardiopulmonary bypass. Four different bypass pump-priming solutions were used.

From The Regional Cardiothoracic Unit, Freeman Hospital, Freeman Road, Newcastle-Upon-Tyne, and The Department of Metabolic Medicine and Clinical Biochemistry, University of Newcastle-Upon-Tyne, Newcastle-Upon-Tyne, United Kingdom.

C. K. M. was supported by the Newcastle Area Scientific and Research Committee.

Additional support was provided by the Lesley Scott Memorial Fund (now the Childrens' Heart Unit Fund)

Received for publication Aug. 6, 1984

Accepted for publication Sept 17, 1984

Address for reprints: Martin J Elliott, M.D., F.R.C.S., Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London, WC1N 3JH, United Kingdom.

## Patients and methods

Twenty-four adult patients undergoing elective open valve operations and taken sequentially from the waiting

**Table I.** *Composition of the bypass pump-priming fluid used in each group (prime volume = 2.5 L)*

| *Priming fluids* | *Composition* |
|---|---|
| *Group A:* Hartmann's solution (Ringer's lactate) and 5% dextrose | |
| Dextrose (gm/L) | 25 |
| $Na^+$ (mmol/L) | 66 |
| $K^+$ (mmol/L) | 2.5 |
| $Ca^{++}$ (mmol/L) | 56 |
| $Cl^-$ (mmol/L) | 56 |
| Lactate (mmol/L) | 15 |
| *Group B:* Hartmann's solution (Ringer's lactate) | |
| $Na^+$ (mmol/L) | 131 |
| $K^+$ (mmol/L) | 5 |
| $Ca^{++}$ (mmol/L) | 2 |
| $Cl^-$ (mmol/L) | 111 |
| Lactate (mmol/L) | 29 |
| *Group C:* Plasmalyte 148 | |
| $Na^{++}$ (mmol/L) | 140 |
| $K^+$ (mmol/L) | 5 |
| $Ca^{++}$ (mmol/L) | 0.5 |
| $Mg^{++}$ (mmol/L) | 1.5 |
| $Cl^-$ (mmol/L) | 80 |
| Acetate (mmol/L) | 27 |
| *Group D:* Solution 11 | |
| Dextrose (gm/L) | 25 |
| $Na^{++}$ (mmol/L) | 102 |
| $K^+$ (mmol/L) | 5 |
| $Ca^{++}$ (mmol/L) | 2.5 |
| $Mg^{++}$ (mmol/L) | 1 |
| $Cl^-$ (mmol/L) | 107 |
| Gluconate (mmol/L) | 5 |
| Phosphate (mmol/L) | 1 |

list of one cardiac surgeon (M. P. H.) were studied. Written, informed consent was obtained from the patients, the protocol having been approved in advance by the Newcastle Health Authority Ethical Committee. Patients with known ischemic heart disease, those taking beta adrenergic blocking agents, those with known endocrine or metabolic disease or an abnormal glucose tolerance test on admission, and those patients with known hepatic or renal disease were excluded from the study.

The 24 patients were randomly allocated to receive one of four different pump-priming fluids during cardiopulmonary bypass. These priming fluids were chosen on the basis of data obtained from a preliminary survey in which a questionnaire was sent to all cardiac surgical units in the United Kingdom. The four primes used in this study were those most commonly in use at that time (1982) in the United Kingdom (Table I).

*Group A* consisted of six patients undergoing cardiopulmonary bypass with a prime consisting of equal volumes of Hartmann's (Ringer's lactate) solution and 5% dextrose in water.

*Group B* consisted of six patients undergoing cardiopulmonary bypass with a Hartmann's solution (Ringer's lactate) prime.

*Group C* consisted of six patients undergoing cardiopulmonary bypass with a prime composed of Plasmalyte-148 (Travenol, Thetford, United Kingdom).

*Group D* consisted of six patients undergoing cardiopulmonary bypass with a prime composed of Solution 11 (Travenol).

Clinical details of the patients studied are given in Table II. The groups were matched in all respects. All patients made uneventful recoveries from the operation.

Anesthetic technique was standardized as follows: Premedication consisted of papaveretum 11.75 mg/m² and hyoscine 0.25 mg/m² given intramuscularly 1 hour before the operation. Anesthesia was induced with intravenous thiopentone 120 mg/m², droperidol 11.75 mg/m², and phenoperidine 2.4 mg/m², and paralysis was produced by pancuronium 4.7 mg/m². Anesthesia was maintained with nitrous oxide and oxygen with intermittent phenoperidine. Further pancuronium was added as required to permit intermittent positive-pressure ventilation.

Perfusion technique was also standardized. Cardiopulmonary bypass was conducted at 28° C (venoarterial cooling) at a flow rate of 2.4 L/m²/min, which was maintained at all temperatures. A Travenol membrane oxygenator was used in each case. Pulsatile flow was generated with a Stöckert (Stöckert Instrumente, Munich, Federal Republic of Germany) pulsatile roller-pump system set to deliver for 50% of the cycle at 90 beats/min, whenever the left ventricle was not ejecting blood into the aorta. The prime volume of the system was 2.5 L in each case.

No glucose-containing fluids were infused or used as flushes in the pressure-monitoring lines. All operations were performed by the same surgeon (M. P. H.). Cardioplegic arrest was used in each case and was achieved with a crystalloid solution at 4° C.* All excised valves were replaced by Ionescu-Shiley bovine pericardial xenografts.

**Blood sampling.** Blood samples were drawn according to the regimen shown in Table III. At every sample point the concentrations of the following were estimated:

*Potassium chloride 1.865 gm/L., dextrose 2 gm/L., sodium chloride 6.32 gm/L., and sodium bicarbonate (8.4%) 12 ml/L.

**Table II.** *Clinical details of patients in the study*

| | *Prime* | | | |
|---|---|---|---|---|
| | *Plasmalyte 148* | *Solution 11* | *Hartmann's solution* | *Ringer's lactate dextrose* |
| No. | 6 | 6 | 6 | 6 |
| Age (yr) ± SEM | 56 ± 1.7 | 52 ± 4 | 59.8 ± 3.3 | 50 ± 5 |
| Sex | 4 M, 2 F | 3 M, 3 F | 2 M, 4 F | 4 M, 2 F |
| Height (m) ± SEM | 1.71 ± 0.02 | 1.65 ± 0.004 | 1.59 ± 0.02 | 1.71 ± 0.03 |
| Weight (kg) ± SEM | 67 ± 4.6 | 67 ± 5.3 | 60.1 ± 1.1 | 60 ± 3.4 |
| Surface area ($m^2$) ± SEM | 1.77 ± 0.07 | 1.74 ± 0.08 | 1.63 ± 0.02 | 1.68 ± 0.07 |
| Operation | MV, AV, MV, MV, MV, MV | AV, AV, MV AV, MV, AV | MV, MV, MV, MV, AV, MV | MV, MV, DV, MV, AV, AV |

*Legend.* AV, Aortic valve replacement. MV, Mitral valve replacement. DV, Double valve replacement. SEM, Standard error of the mean.

insulin, cortisol, glucagon, growth hormone, glucose, lactate, pyruvate, alanine, glycerol, and 3-hydroxybutyrate.

**Assays.**

*Insulin.* Serum insulin concentrations were estimated by the method described by Soeldner and Slone,[8] a modified double antibody radioimmunoassay technique.

*Cortisol.* Total serum cortisol levels were also determined by radioimmunoassay[9] and performed by the Northern Regional SAS Laboratory.

*Glucagon.* Glucagon estimations were performed by a wick-chromatography radioimmunoassay technique.[10] The technique was modified to be specific for pancreatic glucagon and was corrected for extract damage of labeled glucagon.

*Growth hormone.* Growth hormone was estimated by a double antibody system using a Wellcome (rabbit) antiserum to human growth hormone.

*Glucose, lactate, pyruvate, glycerol, alanine, and 3-hydroxybutyrate.* Concentrations of these metabolites were estimated in perchloric acid extracts of whole blood by an enzymatic fluorometric continuous-flow assay as described by Lloyd and associates.[11]

**Statistics.** Student's t test, paired and unpaired, was used to evaluate the significance of differences within and between groups, respectively. All p values are two-tailed. Values given in the text are means ± standard errors of the mean unless otherwise indicated.

**Table III.** *The intermittent blood sampling regimen used in the study*

| *Sample No.* | *Time of event* |
|---|---|
| 1 | One day preoperatively, 8:00 A.M. |
| 2 | One day preoperatively, 6:00 P.M. |
| 3 | Operative day, 8:00 A.M. |
| 4 | Operative day, 5 min after induction of anesthesia |
| 5 | Operative day, 5 min after skin incision |
| 6 | Operative day, 5 min after heparin |
| 7 | Operative day, 5 min after onset of CPB |
| 8 | Operative day, 15 min after onset of CPB |
| 9 | Operative day, 30 min after onset of CPB |
| 10 | Operative day, 60 min after onset of CPB |
| 11 | Operative day, 5 min before end of CPB |
| 12 | Operative day, 5 min after protamine |
| 13 | Operative day, 1 hr postoperatively |
| 14 | Operative day, 2 hr postoperatively |
| 15 | Operative day, 4 hr postoperatively |
| 16 | Operative day, 6 hr postoperatively |
| 17 | Operative day, 8 hr postoperatively |
| 18 | One day postoperatively, 8:00 A.M. |
| 19 | One day postoperatively, 12:00 noon |
| 20 | One day postoperatively, 6:00 P.M. |
| 21 | Two days postoperatively, 8:00 A.M. |
| 22 | Two days postoperatively, 6:00 P.M. |
| 23 | Three days postoperatively, 8:00 A.M. |
| 24 | Three days postoperatively, 6:00 P.M. |
| 25 | Four days postoperatively, 8:00 A.M. |
| 26 | Four days postoperatively, 6:00 P.M. |
| 27 | Seven days postoperatively, 8:00 A.M. |

## Results

All hormone and intermediary metabolite concentrations were within the laboratory reference ranges preoperatively.

**Hormones.** The results of the hormone assays are depicted graphically in Figs. 1 to 4.

***Insulin*** **(Fig. 1). No significant change in serum insulin concentration occurred in any group until the start of the operation. By sample 6 (taken 5 minutes before the onset of cardiopulmonary bypass), however, insulin concentration had fallen significantly ($p < 0.05$) from the initial preoperative value of 10.5 ± 2.9 μU/ml**

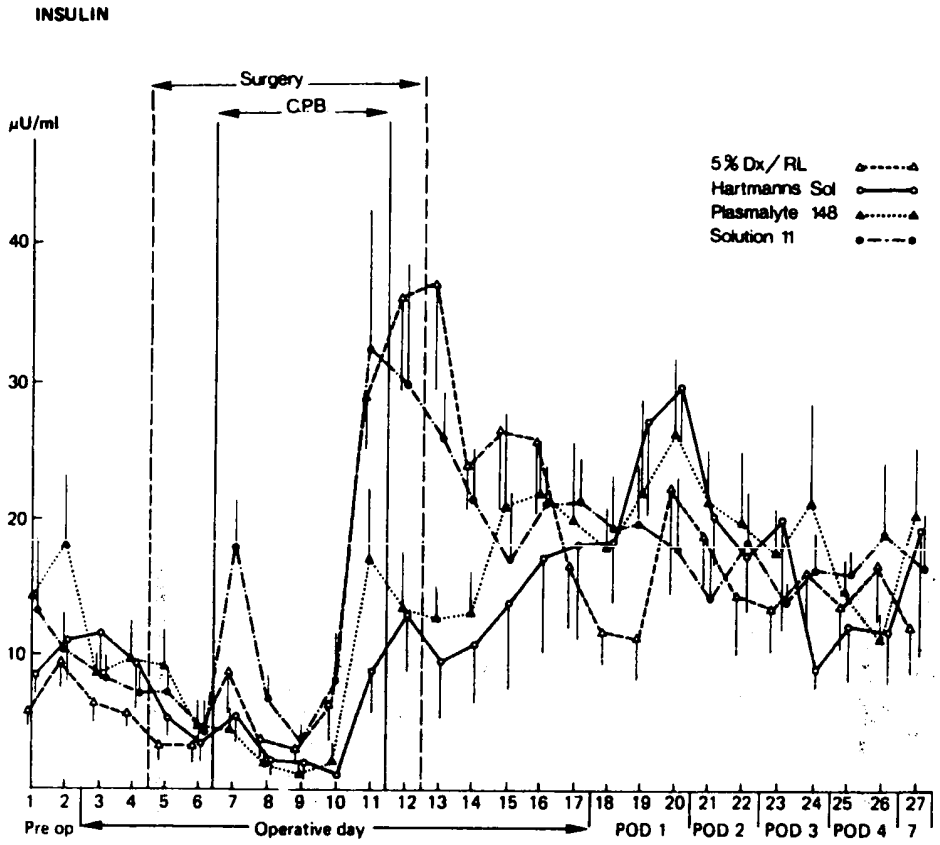


**Fig. 1.** Serum insulin levels (μU/ml) during and after cardiopulmonary bypass with four different pump-priming solutions. *CPB*, Cardiopulmonary bypass. *Dx*, Dextrose. *RL*, Ringers lactate. *POD*, Postoperative days. Sample numbers as in Table III. *Vertical lines* at each sample point represent standard errors of the mean.

to 4.0 ± 1.2 μU/ml. The onset of cardiopulmonary bypass was associated with a rise in insulin concentration in the two groups of patients receiving glucose-containing primes. This rise was significant, however, only in Group D (Solution 11), in whom the insulin concentration rose from 4.2 ± 1.2 μU/ml to 17.7 ± 2.0 μU/ml ($p < 0.05$). Thereafter, insulin concentrations fell in all four groups such that after half an hour of hypothermic bypass they were below fasting values in all groups. Insulin concentration remained below fasting levels throughout the hypothermic phase of bypass. However, after rewarming (as indicated by sample 11, taken 5 minutes before the end of bypass), insulin concentration rose in all four groups. The rise in insulin concentration of 23.2 ± 5.0 μU/ml observed in the groups allocated to receive glucose-containing primes was significantly greater ($p < 0.01$) than the rise of 10.0 ± 3.5 μU/ml observed in those receiving glucose-free primes. There was no significant difference between the insulin concentrations observed in the two groups receiving glucose-containing primes (Groups A and D), nor was there any difference between the insulin concentrations observed with the two non-glucose-containing primes (30.4 ± 7.4 and 12.5 ± 4.4 μU/ml, respectively). The difference in insulin concentrations that was evident between the two sets of pump primes (i.e., glucose and non-glucose-containing) had disappeared 2 hours after the end of the operation. From this stage of the study until the seventh postoperative day, there was no significant difference in insulin concentrations among the four groups. However, throughout this period, fasting insulin concentrations were significantly greater ($p < 0.05$) than preoperative fasting insulin concentrations. Mean fasting values on the seventh postoperative day were 17.0 ± 5.2 μU/ml for all four groups, compared with a preoperative mean value of 10.5 ± 2.0 μU/ml.

*Cortisol* (Fig. 2). There was no significant difference between groups in either the magnitude or pattern of change of serum cortisol concentrations at any stage in the course of the study.

Cortisol concentrations began to rise in all four

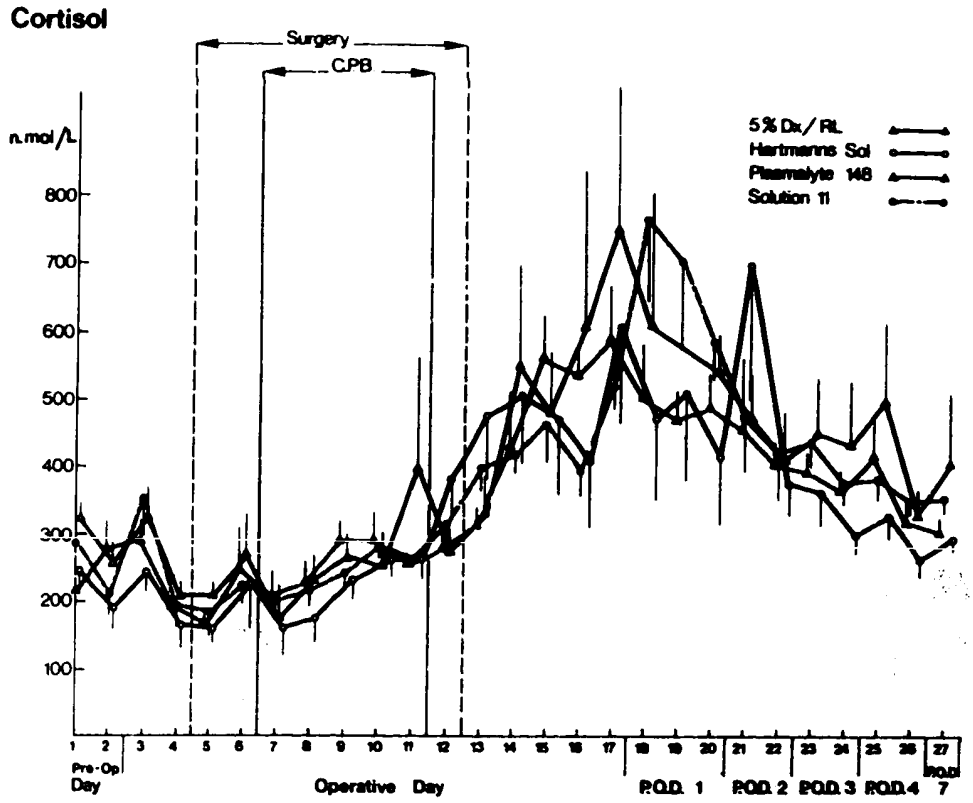


**Fig. 2.** Serum cortisol levels (nU/ml) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 1.

groups shortly after the start of the operation, from immediate preoperative values of 194 ± 23 nmol/L to values of 241 ± 49 nmol/L, 5 minutes after heparinization. The onset of cardiopulmonary bypass was associated with a marked fall in serum cortisol concentration in all four groups. This was presumably due to the dilutional effect of the prime. During cardiopulmonary bypass and throughout the period of hypothermia, cortisol concentrations continued to rise steadily in all groups to reach a mean value for all four groups of 608 ± 117 nmol/L by 6 hours postoperatively. Cortisol values remained at these high levels until the morning of the first postoperative day, after which they fell gradually during the next few days. However, cortisol levels remained significantly elevated throughout the course of the study and were still significantly greater than preoperative values on the seventh postoperative day ($p < 0.05$), when the mean for the four groups was 352 ± 44 nmol/L.

*Glucagon* (Fig. 3). There was no significant difference in blood glucagon concentration among any of the groups at any stage of the study. Glucagon concentrations were not significantly different from preoperative values in any group until 4 hours postoperatively. Thereafter, glucagon concentrations began to rise steadily in all groups, peaking at 148 ± 25 ng/L on the evening of the first postoperative day. From this point onward, there was a gradual fall in glucagon concentrations until the seventh postoperative day, by which time values were no longer significantly elevated compared with preoperative values.

*Growth hormone* (Fig. 4). The results of growth hormone estimations are less clear-cut than the foregoing, but there were no significant differences among the four groups at any stage. Although the graphically presented data in Fig. 4 demonstrate a clear rise in growth hormone concentration during the operation, they belie the fact that there was a rather unusual distribution of results. Irrespective of the priming fluid used, there appeared to be two groups of patients: those who produced high levels of growth hormone during the operation and those who did not. Similar observations have also been reported by McDonald and colleagues[12] and by ourselves (M. J. Elliott, M.D. Thesis, University of Newcastle-Upon-Tyne). Such a distribution can be demonstrated by separating those patients who pro-

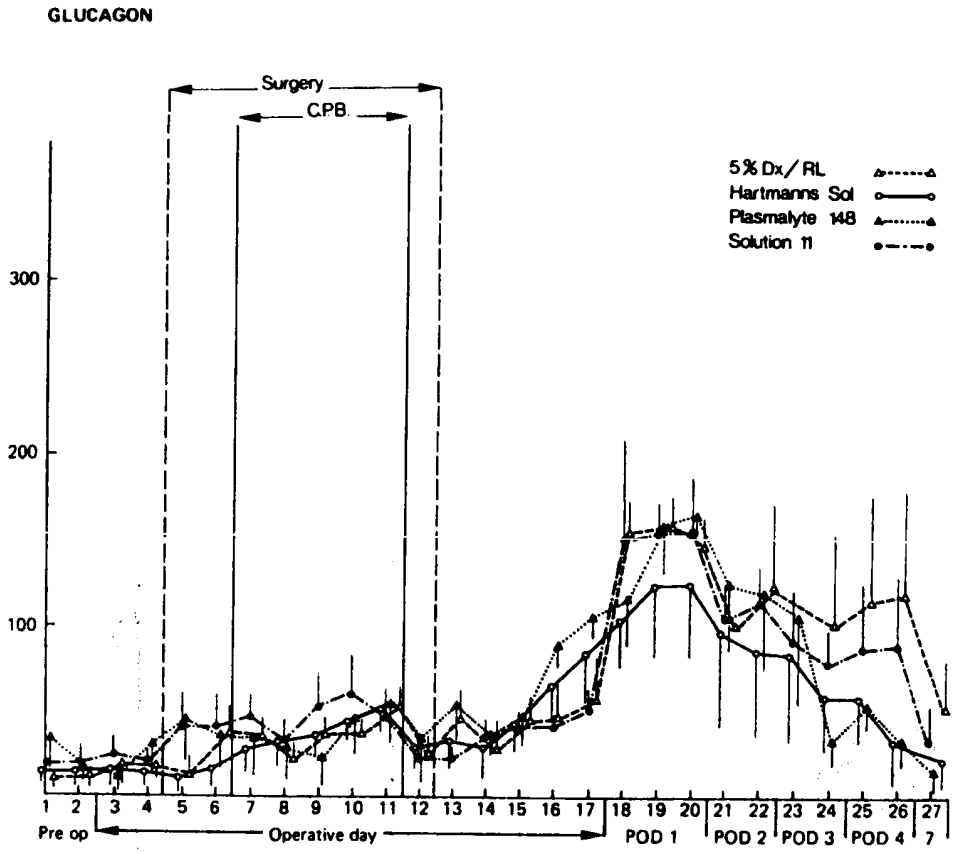


**Fig. 3.** Blood glucagon levels during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 1.

duced growth hormone concentrations of greater than 25 mU/L at any stage in the study from those who did not (Table IV).

**Intermediary metabolites.** The results of the assays of glucose and other intermediary metabolites are expressed graphically in Figs. 5 to 10.

*Glucose* (Fig. 5).* There was no significant change in blood glucose concentration in any group until the onset of cardiopulmonary bypass. Thereafter, in those two groups allocated to receive glucose-free primes (Groups B and C), blood glucose concentrations rose steadily during bypass to values of 10.0 ± 0.2 mmol/L. This degree of glycemia was maintained for the remainder of the operative day. Blood glucose concentrations remained significantly ($p < 0.05$) elevated above preoperative values until the third postoperative day.

When glucose-containing primes were used, however (Groups A and D), there was a dramatic rise in blood glucose concentration after institution of cardiopulmonary bypass. Glucose concentrations of between 25 and 30 mmol/L were observed within 5 minutes of the onset of bypass, and these were sustained throughout the period of extracorporeal circulation. After the end of bypass, blood glucose concentrations fell rapidly in Groups A and D, such that by 4 hours postoperatively there was no significant difference of glucose concentration among the four groups. Thereafter, the pattern of blood glucose concentration change was similar in Groups A and D to that already described for Groups B and C.

*Lactate* (Fig. 6). There were no significant differences in lactate concentrations among any of the four groups until the onset of cardiopulmonary bypass. In the two groups allocated to receive lactate-free primes (Groups C and D), there was no significant alteration in lactate concentration in relation to the onset of cardiopulmonary bypass. During bypass, however, there was a steady rise in lactate concentration in these two groups to levels of 1.63 ± 0.19 mmol/L in Group C and 1.82 ± 0.18 mmol/L in Group D 5 minutes before the end of

*To convert mmol/L to mg/dl multiply by 18.

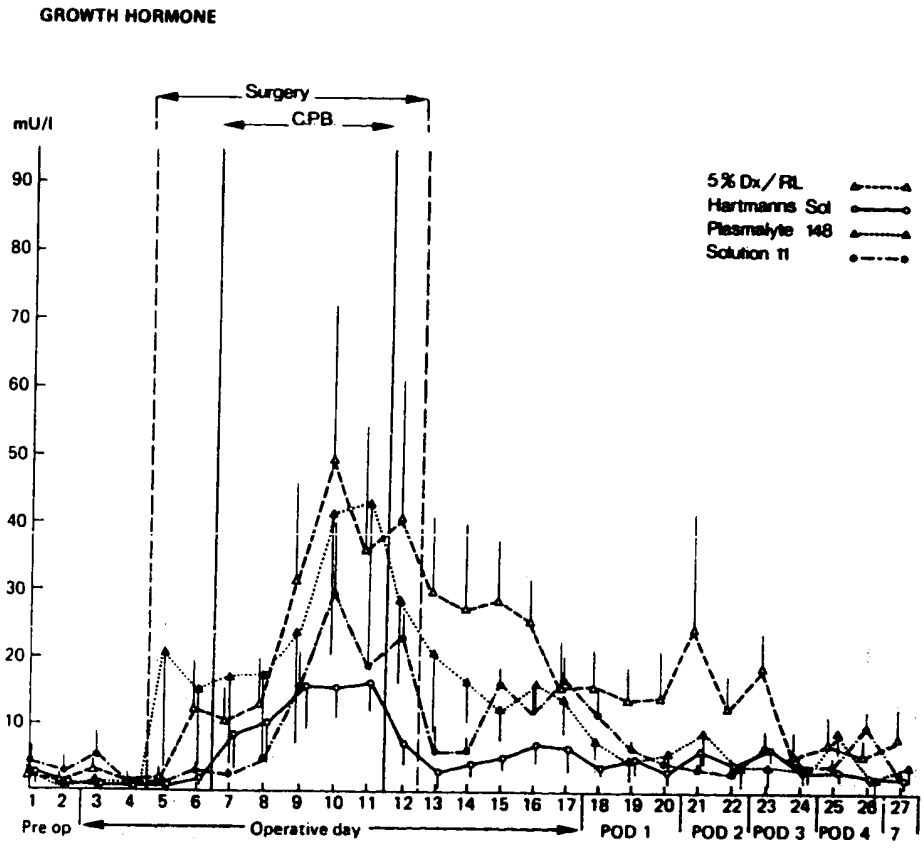


**Fig. 4.** Serum growth hormone levels (mU/L) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 1.

cardiopulmonary bypass. Thereafter, lactate levels continued to rise in these two groups, to peak between 1 and 2 hours postoperatively at 1.82 ± 0.14 mmol/L and 2.34 ± 0.26 mmol/L, respectively.

In the two groups allocated to receive primes containing lactate (Groups A and B), the pattern was different. In Group B (Hartmann's solution), lactate concentrations rose rapidly in association with the onset of bypass from 1.02 ± 0.26 mmol/L to 3.42 ± 0.47 mmol/L 5 minutes after the onset of bypass. These high levels were sustained throughout cardiopulmonary bypass but fell rapidly during the immediate postoperative hours. In Group A (5% dextrose plus Hartmann's solution), blood lactate concentration was observed to rise in association with the onset of bypass, although this rise was of smaller magnitude than that seen in Group B. Lactate levels rose from 0.98 ± 0.14 mmol/L to 2.1 ± 0.25 mmol/L 5 minutes after the onset of cardiopulmonary bypass. Lactate concentrations did not change significantly throughout the course of cardiopulmonary bypass but continued to rise in this group to peak 2 hours postoperatively at 3.25 ± 0.33 mmol/L. By 4 hours postoperatively, however, lactate concentrations were not significantly different in any of the four groups.

**Table IV.** ***Number of patients in whom growth hormone did and did not reach a peak of 25 mU/L***

| | *No. of patients* | |
|---|---|---|
| | *>25 mU/L* | *<25 mU/L* |
| Group A: Hartmann's solution (Ringer's lactate) and 5% dextrose | 4 | 2 |
| Group B: Hartmann's solution (Ringer's lactate) | 2 | 4 |
| Group C: Plasmalyte 148 | 3 | 3 |
| Group D: Solution 11 | 3 | 3 |

*Pyruvate* (Fig. 7). Pyruvate concentration changes mirrored those of blood lactate, and by 2 hours postoperatively there was no significant difference between the two groups. This similarity of pattern was reflected in lactate:pyruvate ratios (not shown).

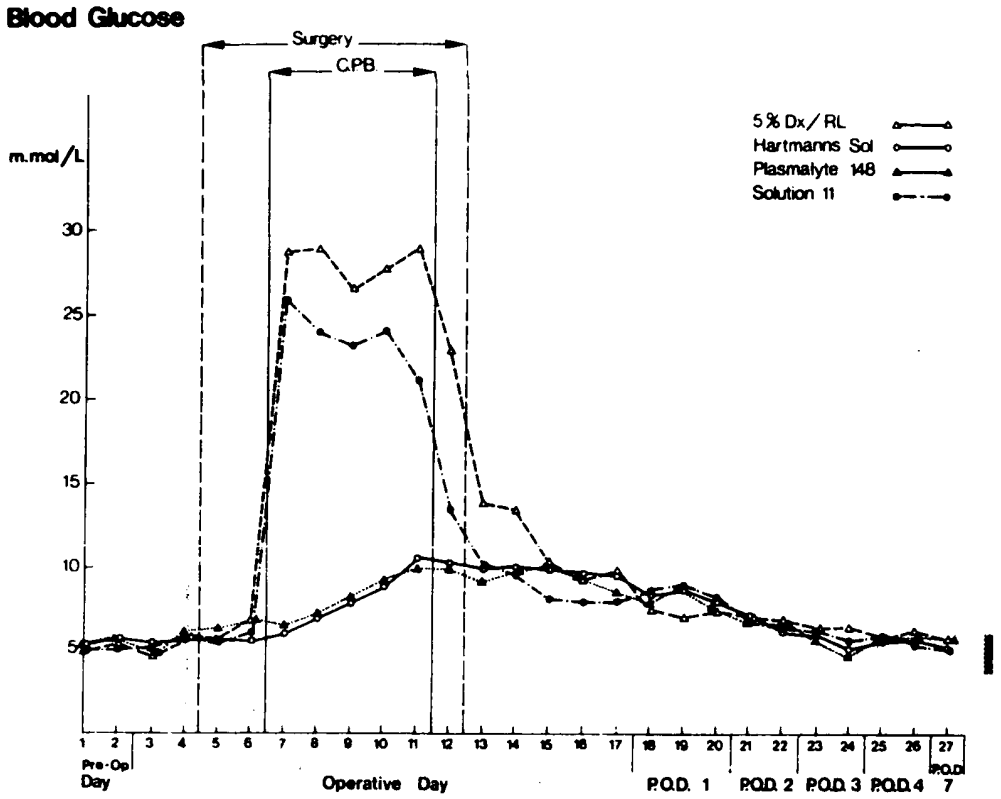


**Fig. 5.** Blood glucose concentrations (mmol/L) during and after cardiopulmonary bypass with four different pump-priming solutions (mmol/L). *Key* as for Fig. 1, but error bars ommitted for clarity. *Solid bar* to the right of the graph represents the normal fasting range. To convert mmol/L to mg/dl multiply by 18.

*Glycerol* (Fig. 8). There was no significant difference in glycerol concentrations between groups at any stage of the study. All four groups showed a similar pattern of response. There was a rise in glycerol concentration of approximately equal magnitude in all four groups in association with systemic heparinization (between samples 5 and 6) from 0.100 ± 0.017 mmol/L to 0.190 ± 0.036 mmol/L. Blood glycerol concentrations remained at these elevated values (which were significantly greater [$p < 0.05$] than preoperative values) throughout cardiopulmonary bypass, but fell sharply in association with the infusion of protamine after completion of cardiopulmonary bypass (between samples 11 and 12). Thereafter, glycerol concentrations were not seen to be significantly different from preoperative values.

*Alanine* (Fig. 9). There was no significant difference among the groups at any stage in the study in terms of blood alanine concentrations. Alanine concentrations fell significantly in all groups ($p < 0.05$) on induction of anesthesia. Values for the whole group fell from 0.33 ± 0.04 mmol/L to 0.26 ± 0.04 mmol/L. Thereafter, there was a gradual increase in alanine levels, being unaffected by skin incision or the institution of cardiopulmonary bypass. On the first postoperative day, there was a transient peak in alanine concentrations in all four groups. This peak corresponded in timing to the rises in both serum cortisol and blood glucagon concentrations. Blood alanine concentrations were not significantly different from preoperative values at any stage postoperatively.

*3-Hydroxybutyrate* (Fig. 10). The pattern of change for 3-hydroxybutyrate in the three groups was not so consistent as those described for the other intermediary metabolites. In Groups A, B, and C, 3-hydroxybutyrate concentrations rose steadily from the induction of anesthesia (samples 3 and 4) to peak values at or shortly after the end of the operation. Subsequently, 3-hydroxybutyrate concentrations fell rapidly such that they were not significantly different from preoperative values by 6 hours postoperatively. However, the patients in Group D (Solution 11) demonstrated a completely different pattern of response. 3-Hydroxybutyrate concentrations in this group did not rise at any stage in the study, after induction of anesthesia. Thus, Group D patients

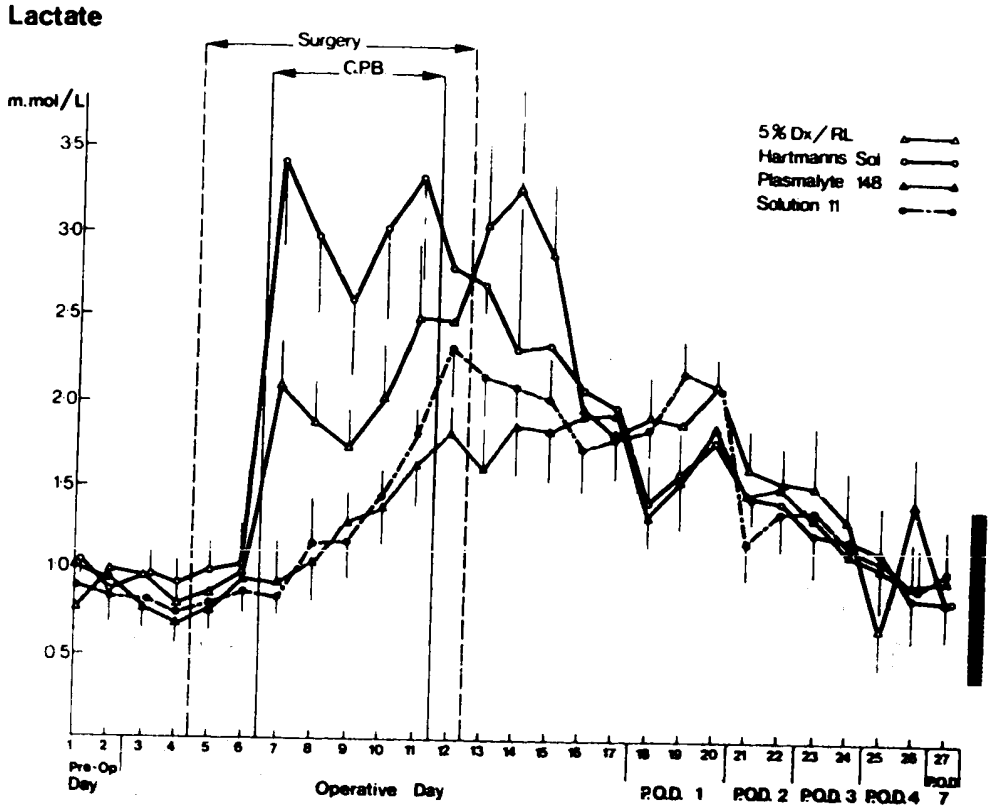


Fig. 6. Blood lactate concentrations (nmol/L) during and after cardiopulmonary bypass, with four different pump-priming solutions. *Key* as for Fig. 5.

behaved differently from the remaining groups *before* the insitution of cardiopulmonary bypass. It is difficult to explain why this group of patients should have behaved differently.

## Discussion

This study has demonstrated that, after 4 hours postoperatively, the endocrine and intermediary metabolic response to cardiac operation is unaffected by the nature of the crystalloid bypass pump-priming fluid. The endocrine and metabolic changes occurring before that time appear to be directly related to the glucose and lactate content of the prime. These findings may account for some of the disparities that are apparent between various other reports of the metabolic response to cardiac operation.[1, 2, 6, 7, 11-13]

The glucose load to which Groups A and D were subjected resulted in a number of interesting changes. First, blood glucose concentrations during bypass were very high (>22 mmol/L). Second, after the onset of bypass and before systemic core-cooling to 28° C was complete, a transient rise in serum insulin concentrations was observed. This rise suggests that the glucose load had stimulated pancreatic beta cell activity, which was subsequently suppressed by the fall in body temperature. Similar observations have been made by Cambridge workers studying high-glucose primes (J. Ruddick, personal communication). After cooling to 28° C and before rewarming, serum insulin concentrations remained low despite the high blood glucose concentrations described earlier. Similar observations have been made by others[1, 13] and may be attributed to the effects of hypothermia and high circulating norepinephrine levels. Serum insulin concentrations rose rapidly in all groups in association with rewarming after hypothermic bypass, and blood glucose concentrations fell rapidly after completion of cardiopulmonary bypass. These findings suggest that hypothermia is the major factor in the inhibition of insulin release observed during cardiopulmonary bypass.

In the two groups of patients receiving no glucose in their pump primes (Groups B and C), there was, during bypass, a steady and equal rise in blood glucose to around 10 mmol/L at the end of bypass. In the absence of infused glucose, this rise in blood glucose concentration must represent endogenous glucose production.

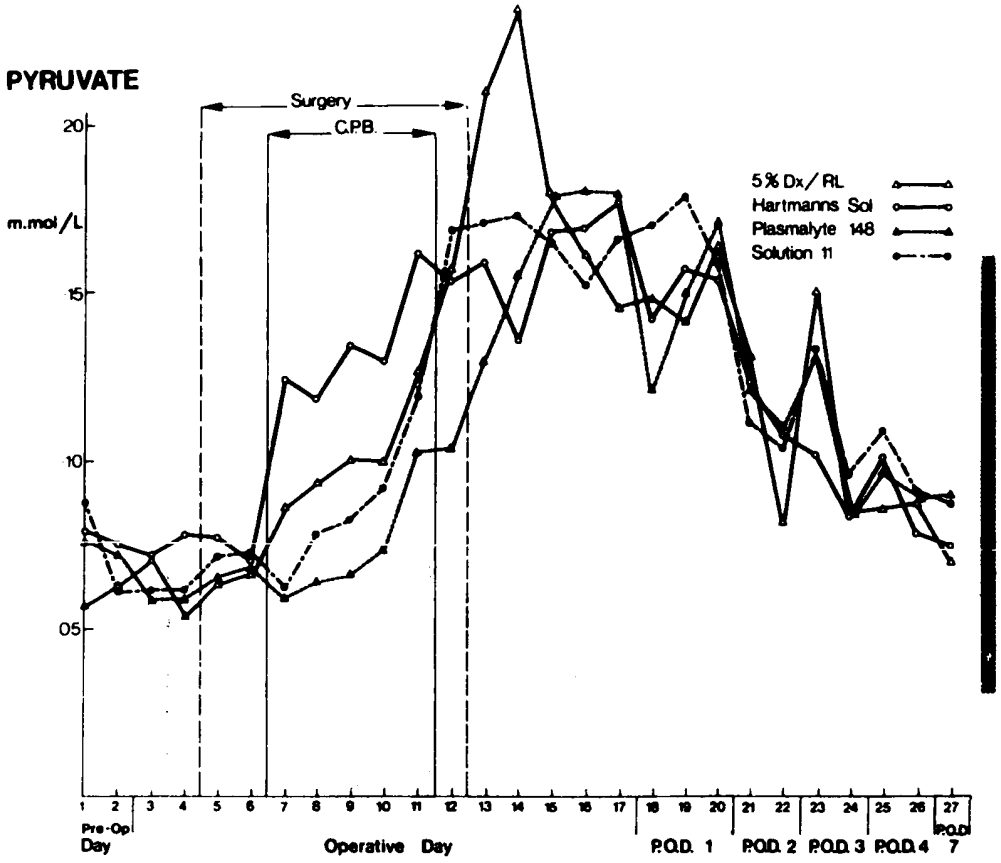


**Fig. 7.** Blood pyruvate concentrations (mmol/L) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 5.

Certainly the high catecholamine concentrations known to occur during cardiopulmonary bypass[3, 14-16] would be expected to increase the rates of both gluconeogenesis and glycogenolysis, particularly in the absence of inhibition by insulin.[17]

The postoperative phase of the study was associated, in all four groups, with sustained but mild hyperglycemia accompanied by hyperinsulinemia. Such an apparently inappropriate relationship has been described following both operation and trauma and has been attributed to insulin resistance consequent upon a post-receptor defect.[18] This has not been confirmed in relation to cardiac operations but is currently under investigation in our unit.

The alterations in lactate concentrations observed during cardiopulmonary bypass in this study may be attributed almost entirely to the lactate content of the pump-priming fluid. It is of interest that no differences in blood glucose concentration were observed during bypass between the two non–glucose-containing primes (Groups B and C). Thomas and Alberti[19] have reported a significant gluconeogeneic effect of infused lactate in diabetic patients undergoing general operations. The observation that glucose concentrations were not significantly greater in Group B (lactate-containing prime) than in Group C patients (non–lactate-containing) during cardiopulmonary bypass and conditions of relative insulin lack suggests that the lactate load in Group B patients was not significantly gluconeogeneic. The relatively high lactate concentrations observed in all groups shortly after the end of operation are likely to be explained by the known effects of catecholamines on glycolytic flux.[16, 17]

Glycerol concentrations were but little affected by bypass and operation. There was, however, a small but significant ($p < 0.05$) rise in blood glycerol concentrations in association with heparinization and a fall of similar degree in association with administration of protamine. Although it is tempting to ascribe this observation to an increased rate of lipolysis in association with heparin activation of lipoprotein lipase,[13, 20, 21] the value of using blood glycerol concentrations as an

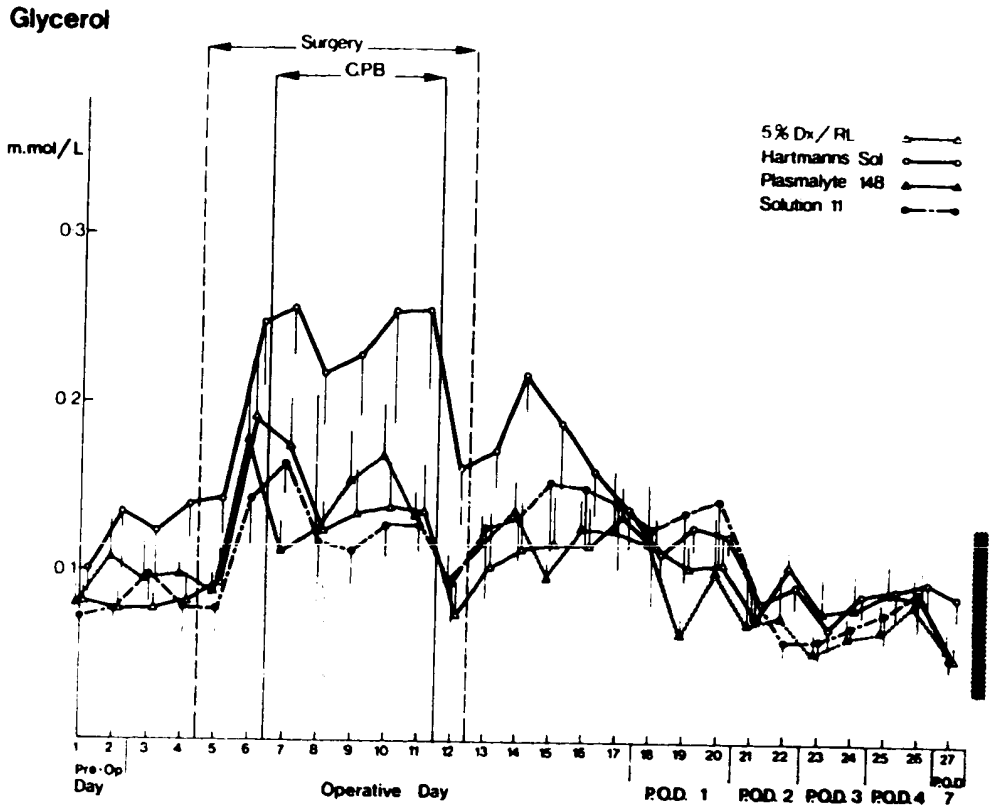


Fig. 8. Blood glycerol concentrations (mmol/L) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 5.

index of lipolysis has been questioned. Carpentier and associates[22] have shown that although blood glycerol concentrations are proportional to glycerol turnover in normal man, the relationship is lost after trauma. However, glycerol concentrations, like those of the principal amino acid gluconeogeneic precursor, alanine, were unaffected by the nature of the prime.

3-Hydroxybutyrate values did seem to be affected by the nature of the pump-priming fluid, in that those patients receiving Solution 11 did not experience the same rise in 3-hydroxybutyrate concentrations that was observed in the other three groups during the operations. We are unable to explain this finding. The changes observed are unlikely to be due entirely to the prime, since 3-hydroxybutyrate values in the patients receiving Solution 11 were significantly lower than those observed in the other groups *before* the onset of bypass.

It is also evident from the data presented that the endocrine response to cardiac operation, as judged by cortisol, glucagon, and growth hormone, was unaffected by the pump prime. This is perhaps surprising in view of the variations in concentrations of such metabolically active substrates as glucose and lactate. We may conclude, however, that the glucose and lactate loads in the prime did not contribute an additional stimulus to the secretion of these hormones.

Certain other observations, however, may be made concerning the cortisol results. In all four groups of patients, there was a small but significant rise in serum cortisol concentrations during hypothermic pulsatile cardiopulmonary bypass. This finding is similar to that reported by Taylor and associates[6] in a group of patients subjected to bypass using similar techniques of pulsatility, although at normothermia. Postoperatively, the pattern of cortisol response was similar to that described after general operations,[23] trauma,[24] and cardiac operations.[1] However, the magnitude of that rise (peak cortisol values of 608 ± 117 nmol/L) was less than that reported in other studies. The reasons for this are not clear. However, since cortisol levels have been interpreted as an index of the severity of the stress response,[17] one may speculate that the stress response to operation in these patients was obtunded. Vaughan and colleagues[25] have suggested that a rise in cortisol secretion seen following burns may simply reflect a rise in core temperature, and not be proportional to the degree of

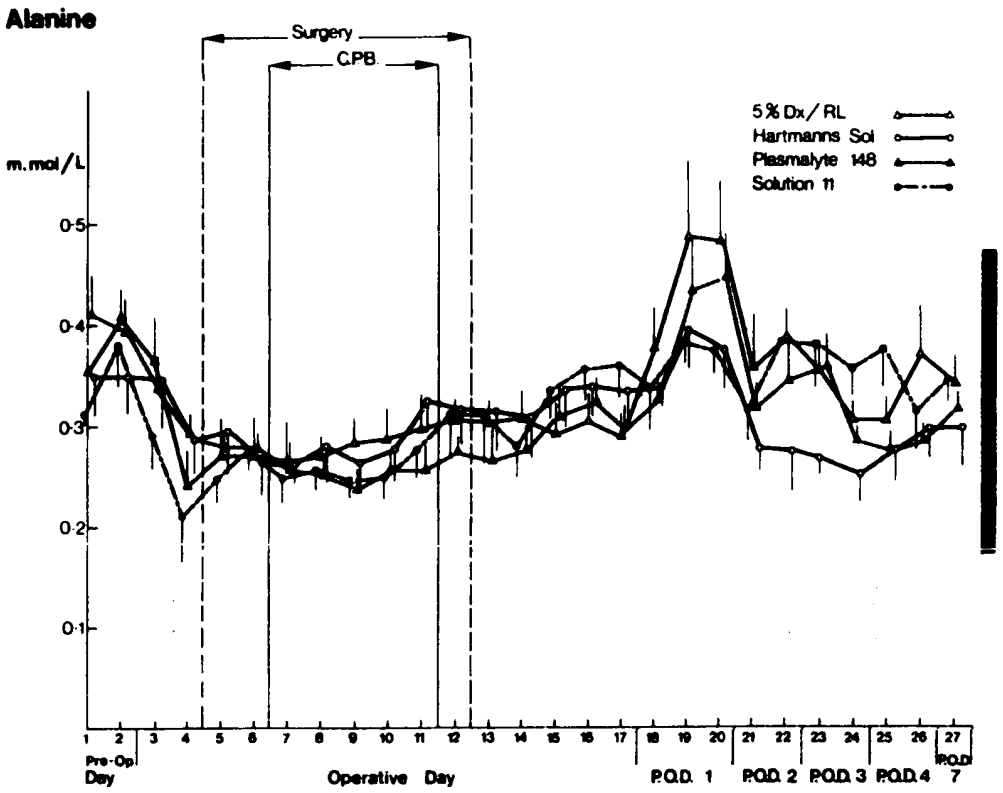


**Fig. 9.** Blood alanine concentrations (mmol/L) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 5.

trauma. However, this is a minority view.[17] The anesthetic technique used was similar to that employed by other workers and thus not likely to suppress cortisol secretion.

There are few previous reports of changes in blood glucagon concentration in relation to cardiac operation, and certainly none with such frequent sampling as was employed in this study.[26,27] The pattern of change in glucagon values observed here conforms with the pattern of change reported after other forms of trauma. Thus, a later rise in glucagon than cortisol was seen, as expected.

The finding of an unusual distribution of growth hormone results is also interesting. Although an apparent, but unexplained, division of adult patients into "high" and "low" responders has been described[15] (M. J. Elliott, M.D. Thesis, University of Newcastle-Upon-Tyne), we[28] have not observed such a distribution in children undergoing cardiac operations, all of whom behaved as high responders. It is interesting to speculate that alterations in growth hormone response to cardiac operation may be age-related.

What importance have these observations for the practical management of patients undergoing cardiopulmonary bypass? The only intermediary metabolic and endocrine effects of variations in the crystalloid component of the prime seem to be related entirely to the glucose and lactate contents of the prime. One should ask, therefore, whether the glucose and lactate loads serve any useful purpose and whether they have any untoward effects.

There is little evidence of any useful purpose being served by glucose in the pump prime. During extracorporeal perfusion, and particularly if hypothermia is employed, glucose utilization is greatly reduced. This, in association with catecholamine-stimulated gluconeogenesis and glycogenolysis, results in a net rise in blood glucose concentration which, although harmless at the relatively low levels seen with non–glucose-containing primes, may be frankly harmful at high concentrations. It has been shown in animal experiments that the presence of hyperglycemia at the time of recovery from cerebral hypoxia/ischemia reduces the likelihood of full recovery from that ischemic event.[29] Since cerebral

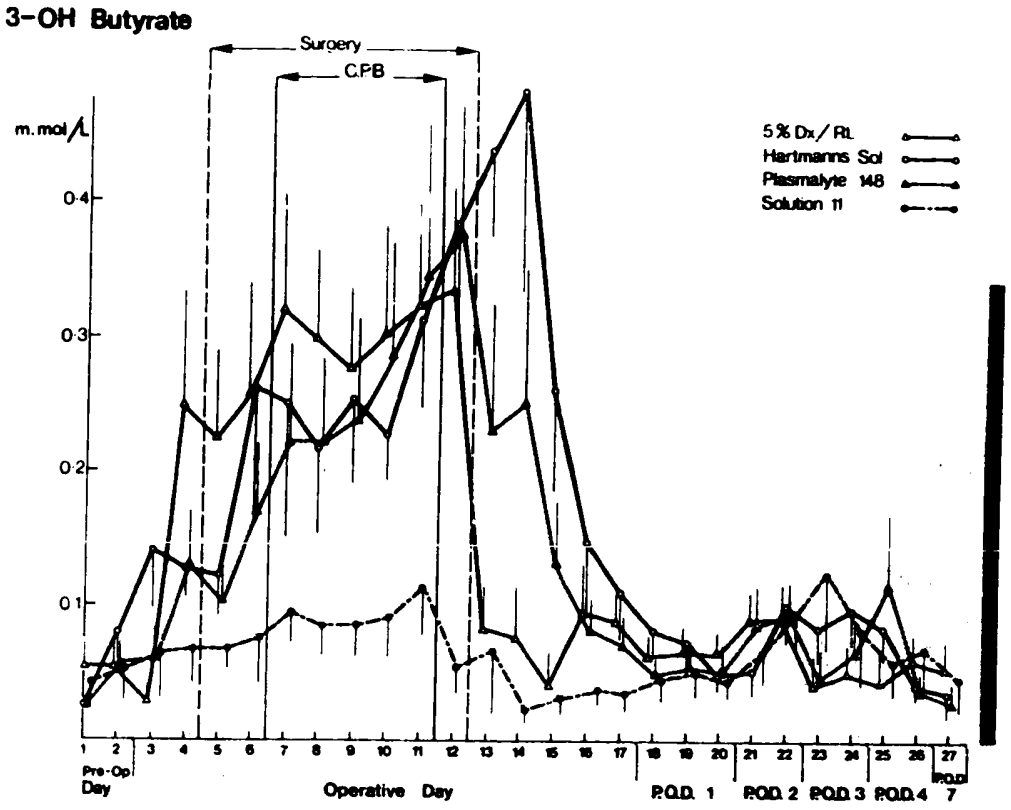


**Fig. 10.** Blood 3-hydroxybutyrate concentrations (mmol/L) during and after cardiopulmonary bypass with four different pump-priming solutions. *Key* as for Fig. 5.

ischemia–related events may be an unwanted effect of cardiac operation with cardiopulmonary bypass, the addition of glucose to the prime seems to be an unnecessary risk. Further, high blood glucose concentrations have been shown to interfere with platelet function in diabetic patients, abnormalities that are corrected by restoration of normoglycemia.[30] Diminished platelet activity is not regarded as a welcome accompaniment of cardiac operation. High blood glucose concentrations may also interfere with white cell function in vitro,[30] although we[31] have not confirmed this in vivo in patients undergoing cardiac operations.

Thomas and Alberti[19] have reported the importance of avoiding lactate infusion in diabetic patients undergoing operation. Although we have not demonstrated any significant gluconeogenetic effect of lactate in this study, we can think of no good reason for its inclusion in the prime. Further, we[32] have established recently that the use of a non–glucose, non–lactate-containing prime is of great value in the management of diabetics undergoing cardiac operations.

This study has thus demonstrated that, after 4 hours postoperatively, the nature of the crystalloid pump prime has no effect on the metabolic or endocrine response to cardiac operation. There appear to be good reasons for the exclusion of glucose and lactate from the pump prime and none for their inclusion. Since we have demonstrated no untoward metabolic consequences, we suggest that a non–glucose, non–lactate-containing fluid should be used as the crystalloid component of the prime for the extracorporeal circuit in cardiopulmonary bypass unless otherwise indicated.

We are indebted to Dr. Hans Ørskov (Aarhus, Denmark) who performed the glucagon estimations, to the Audio Visual Department of the University of Newcastle-Upon-Tyne for preparation of the graphics, and to Miss Sarah Burnett of the Thoracic Unit, The Hospital for Sick Children, Great Ormond Street, London, United Kingdom, for preparation of the manuscript.

## REFERENCES

1. Walsh ES, Paterson JL, O'Riordan JBA, Hall GM: Effect of high-dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. Br J Anaesth 53:1155-1164, 1981

2 Brandt MR, Korshin J, Prange-Hansen A, Hummer L, Nistrop-Madsen S, Rygg I, Kehlet H: Influence of morphine anaesthesia on the endocrine-metabolic response to open-heart surgery. Acta Anaesth Scand **22**:400-412, 1978

3 Philbin DM, Levine FH, Kono K, Coggins CH, Moss J, Slater EE, Buckley M: Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. Circulation **64**:808-812, 1981

4 Philbin DM, Levine FH, Emerson CW, Coggins CH, Buckley MJ, Austen WG: Plasma vasopressin levels and urinary flow during cardiopulmonary bypass in patients with valvular heart disease. The effect of pulsatile flow. J THORAC CARDIOVASC SURG **78**:779-783, 1979

5 Landymore RW, Murphy DA, Kinley CE, Parratt JC, Moffitt EA, Longley WJ, Qirbi AA: Does pulsatile flow influence the incidence of postoperative hypertension? Ann Thorac Surg **28**:261-268, 1979

6 Taylor KM, Wright GS, Reid JM, Bain WH, Caves PK, Walker MS, Grant JK: Comparative studies of cardiopulmonary bypass. II. The effects on adrenal secretion of cortisol. J THORAC CARDIOVASC SURG **75**:574-578, 1978

7 Moffitt EA, Sessler AD, Molnar GD, McGoon DC: Normothermia versus hypothermia for whole-body perfusion. Effects on myocardial and body metabolism. Anesth Analg **50**:505-516, 1971

8 Soeldner JS, Slone D: Critical values in the radioimmune assay of serum insulin using the double antibody technique. Diabetes **14**:771-779, 1965

9 Seth S, Brown LM: A simple radioimmunoassay for plasma cortisol. Clin Chim Acta **86**:109-120, 1978

10 Ørskov H, Thomsen HG, Yde H: Wick-chromatography for rapid and reliable immunoassay of insulin, glucagon and growth hormone. Nature **219**:193-195, 1968

11 Lloyd B, Burrin J, Smythe P, Alberti KGMM: Simple automated fluorometric assays for blood glucose, lactate, pyruvate, alanine, glycerol and 3-hydroxybutyrate. Clin Chem **24**:1724-1729, 1978

12 McDonald RG, Buckler JMH, Deverall PB, Watson DA, Ballint M: Growth hormone and blood glucose concentrations during cardiopulmonary bypass. Br J Anaesth **47**:713-718, 1975

13 Yokota H, Kawashima Y, Takao T, Hashimoto S, Manabe H: Carbohydrate and lipid metabolism in open-heart surgery. J THORAC CARDIOVASC SURG **73**:543-549, 1977

14 Replogle R, Levy M, DeWall RA, Lillehei RC: Catecholamine and serotonin response to cardiopulmonary bypass. J THORAC CARDIOVASC SURG **44**:638-648, 1962

15 Stanley TH, Berman L, Green O, Robertson D: Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary artery operation. Anesthesiology 53:250-253, 1980

Tan GK, Gusson SN, El-Ejr AA, Ramakrixanan KB: Levels of circulating norepinephrine and epinephrine before, during, and after cardiopulmonary bypass in man. J THORAC CARDIOVASC SURG **71**:928-931, 1976

17 Elliott MJ, Alberti KGMM: Carbohydrate metabolism. Effect of preoperative starvation and trauma. Clinics in Anaesthesiol **1**:527-550, 1983

18 Black PR, Brooks DC, Bessey PQ, Wolfe RR, Wilmore DW: Mechanisms of insulin resistance following injury. Ann Surg **196**:420-435, 1982

19 Thomas DJ, Alberti KGMM: Effects of Hartmann's solution during surgery in patients with maturity-onset diabetes. Br J Anaesth **50**:185-190, 1978

20 Hahn PF: Abolishment of alimentary lipemia following injection of heparin. Science **98**:19-20, 1943

21 Roberg J, Carlson LA: Determination of heparin-induced lipoprotein lipase activity in human plasma. Clin Chim Acta **10**:420, 1964

22 Carpentier YA, Nordenstrom J, Robin A, Kinney JM: Glycerol turnover and kinetics of exogenous fat in surgical patients. Symposia, Second European Congress on Parenteral and Enteral Nutrition, PD Wright, MJ Elliott, eds., Acta Chir Scand Suppl **507**:226-237, 1981

23 Allison SP: Changes in insulin secretion during open-heart surgery. Br J Anaesth **43**:138-143, 1971

24 Brandt MR, Kehlet H, Binder C, Hagen C, McNeilly AS: Effect of epidural analgesia on the glucoregulatory endocrine response to surgery. Clin Endocrinol **5**:107-114, 1976

25 Vaughan GM, Becker RA, Allen JP, Goodwin CW Jr, Pruitt BA Jr, Mason AD Jr: Cortisol and corticotrophin in burn patients. J Trauma **22**:263-273, 1982

26 Teramoto T, Fukukei I, Okamura E, Kurahashi H, Hattori Y, Isaji H, Sai S, Kurahashi M: Changes of serum gastrin, amylase, insulin and glucagon during and after open-heart surgery with cardiopulmonary bypass. J Jpn Assoc Thorac Surg **28**:23-29, 1980

27 Kobayashi M, Irisana T, Nakamura C, et al: The study of glucose metabolism, pancreatic endocrine and exocrine in cardiopulmonary bypass. J Jpn Assoc Thorac Surg **28**:1085-1089, 1980

28 Milne EMG, Elliott MJ, Holden MP, Pearson DT, Alberti KGMM: The intermediary metabolic response to open heart surgery with deep hypothermic circulatory arrest in infants of <10 kg body weight. (submitted for publication)

29 Siemkowicz E: Hyperglycaemia in the reperfusion period hampers recovery from cerebral ischaemia. Acta Neurol Scand **64**:207-216, 1981

30 Van Oss CJ: Influence of glucose levels on the in vitro phagocytosis of human neutrophils. Infect Immun 1971, pp 54-59

31 Conroy P, Elliott MJ, Platt P, Pearson DT, Holden MP: Neutrophil function and open-heart surgery in man. The effects of glucose and non-glucose containing pump-priming fluids. (submitted for publication)

32 Elliott MJ, Gill GV, Home PD, Noy GA, Holden MP, Alberti KGMM: A comparison of two regimens for the management of diabetes during open-heart surgery. Anesthesiology **60**:364-368, 1984

33 Batstone GF, Alberti KGMM, Hinks L, Smythe P, Ling

JED, Ward CM, Ely RW, Bloom SR: Metabolic studies in subjects following thermal injury. Burns 2:207-255, 1976

34 Long CL, Schaffel N, Griger JW, Schiller WR, Blackmore WS: Metabolic response to injury and illness. J Parenter Ent Nutr 3:452-456, 1979

35 Stanley TH, Berman L, Green O, Robertson D: Plasma catecholamine and cortisol responses to fentanyl oxygen anesthesia for coronary artery operation. Anesthesiology 53:250-253, 1980

36 Hoar PF, Stone JG, Faltas AN, Bendixcen HH, Head RJ, Berkowitz BA: Hemodynamic and adrenergic responses to anesthesia and operation for myocardial revascularization. J Thorac Cardiovasc Surg 80:242-248, 1980

37 Voisin P, Ronselle D, Guimont C, Drowun P, Stoitz JF: Evaluation of beta-TG level in diabetic patients undergoing artificial pancreas treatment. Thromb Haemost 46:440, 1981